# Cosinor-Based Circadianity of T-Wave Alternans Activity as a Predictor of Sudden Cardiac Death in Heart Failure: a Post-Hoc Analysis of the GISSI-HF Holter Substudy

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## Abstract

*Many studies in the last decades associate the existence of T-wave alternans (TWA) in the ECG to the risk of suffering malignant ventricular arrhythmias and sudden cardiac death (SCD). In this work, 24-hour Holter ECG recordings from 388 patients aged 65±10 years with heart failure were analyzed. Three Holter recordings were acquired for each patient, allowing to assess the evolution of TWA over 1-year period. We measured the index of average alternans (IAA), representing the average TWA activity along the whole recording, using a multilead fully automated method based on periodic component analysis ($\pi$CA) combined with the Laplacian likelihood ratio method (LLRM). The IAA was also measured for in 1- hour intervals, allowing to observe the influence of circadian rhythms on TWA. A circadian pattern was found showing the highest IAA values between 11:00 and 15:00 hours. The cosinor method was applied to adjust a sinusoidal wave to the results, finding that the MESOR (medium value of the adjusted sinusoidal wave) presented significant predictive power of SCD (Hazard Ratio:3.33(1.38-8.06), p=0.008) in the study population.*

## 1. Introduction

Sudden cardiac death (SCD) represents one of the major causes of death in patients with mild-to-severe chronic heart failure (CHF), mainly consequence of malignant arrhythmias. An effective therapy in this cohort is the use of an implantable cardioverter defibrillator (ICD), but the associated risks and low cost-effectiveness makes very important to identify the patients that would benefit the most from this therapy, reducing both the cost for the healthcare systems and the risk for the patients.

T-wave alternans (TWA) is an amplitude, duration or morphology variation of the T-wave every other beat, which reflects temporal and spatial heterogeneity of ventricular repolarization, and is associated to an increased risk of suffering malignant ventricular arrhythmias and SCD [1]. Moreover, previous studies have shown that the long-term averaging of TWA activity in ambulatory recordings is an independent predictor of SCD [2].

The objective of this work was to evaluate the circadian variation of the index of average alternans (IAA) using the cosinor analysis, and to assess the prognostic value of derived parameters for SCD stratification in a heart failure population.

## 2. Study population

The data used in this work belong to the GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nella Insufficienza Cardiaca - Heart Failure) Holter substudy [3, 4]. The study includes 388 patients with heart failure (HF) belonging to New York Heart Association (NYHA) classes II-IV (mild to severe HF).

For each patient, three 24-hour, 12-lead ECG Holter recordings (H12+, Mortara Instrument Inc., Milwaukee, WI, sampling rate 1000 Hz) were available. The second recording was acquired,in average, 3.6 months after the first recording (range: 1.3 to 8.6 months). The third recording was acquired, in average, 12.7 months after the first recording (range: 8.1 to 20.0 months). We will denote the three recordings for the same patient as Holter-1, Holter-2 and Holter-3, respectively.

Patients were followed-up during 3.9 years (interquartile range 3.0-4.5) since the first recording. The cohort included 47 SCD victims (including patients with appropriate ICD discharge), 22 cardiac deaths and 16 deaths by other causes. The patients' characteristics are summarized

in Table 1.

The study protocol was approved by the local Ethics Committees of all participating sites and all patients gave written informed consent.

Table 1. Clinical characteristics of the population. Data are expressed as mean±std.dev. for continuous variables and as number (percentage) for categorical variables.

| **Characteristics** | **n=388** |
|---|---|
| Age (years) | 65±10 |
| Gender (Women) | 70 (18) |
| NYHA class III–IV | 79 (20) |
| Ischaemic cause of HF | 195 (50) |
| Systolic arterial pressure (mmHg) | 125±17 |
| Diastolic arterial pressure (mmHg) | 77±9 |
| LVEF (%) | 33±8 |
| Beta-blockers | 267 (69) |
| Amiodarone | 62 (16) |
| ICD | 14 (3.6) |

NYHA: New York Heart Association; LVEF: Left ventricular ejection fraction; HF: heart failure; ICD: Implantable cardioverter defibrillator

# 3. Methods

## 3.1. Preprocessing

The preprocessing of ECG recordings included heart beat detection using the Aristotle ECG analysis software [5]. Then ECG was then high-pass linear filtering of baseline wander was used to remove baseline variations and low-pass filtered with a cut-off frequency of 15Hz to remove high-frequency noise out of the TWA frequency band. Finally, the filtered ECG was down-sampled to remove redundancy and to reduce computational costs.

## 3.2. TWA estimation

In order to quantify TWA, the index of average alternans (IAA) was computed from the 24-hour ECGs, using a multi-lead, fully-automated method based on periodic components ($\pi$CA) combined with Laplacian likelihood ratio method (LLRM) [2]. ECG signals were divided in segments of 128 consecutive beats (50% overlapped). Segments which did not satisfy a heart rate (HR) and baseline stability imposed criteria (defined in [2]) were discarded in order to consider only suitable segments for the analysis.

In order to estimate the TWA waveform representative of an ECG segment, the method was applied as in [2]: the eight independent leads (V1-V6, I, II) were linearly combined to get a transformed lead whose TWA periodicity (i.e. 2-beat period) was maximized using $\pi$CA [6]. Then, the LLRM [7] was used in the transformed lead to estimate the TWA waveform of each segment, as a result of the median difference between consecutive ST-T complexes of even and odd beats, denoted as $\mathbf{y}_k = [y_k(1) \dots y_k(N)]^T$, with N the number of samples of the ST-T complex of the $k$-th ECG segment of the new combined lead.

Before final averaging of all estimated TWA waveforms, a phase alignment step is needed, since the TWA component present in each $\mathbf{y}_k(n)$ may not have the same alternating phase, and therefore might cancel out when averaging. For this, the dominant waveform of all $\mathbf{y}_k(n)$ was computed and, depending on whether its correlation with each $\mathbf{y}_k(n)$ was positive or negative, $\mathbf{y}^a_k(n)$ maintained or inverted the sign, respectively.

At this point, we can finally obtain the IAA as the mean absolute value of the average waveform of all suitable alternans waveforms $\mathbf{y}^a_k(n)$

$$IAA = \frac{1}{N}\sum_{n=1}^{N}\left|\frac{1}{K}\sum_{k=1}^{K}\mathbf{y}^a_k(n)\right| \quad (1)$$

## 3.3. Cosinor analysis

All physical, behavioural or mental changes which occur in a 24-hour period are known as circadian rhythms. The cosinor analysis adjusts the input data to a sine function based on a least squares method [8]. In order to study circadianity, IAA values were computed each hour by dividing the ECG Holters into 24 1-hour intervals, thus obtaining 24 IAA values for each Holter. In that way, we could observe the variation of IAA along the day.

The cosinor regression model is defined as:

$$y(t) = M + Acos(\frac{2\pi t}{\tau} + \phi) + e(t) \quad (2)$$

where M is the MESOR (acronym of midline estimating statistic of rhythm) which is the mean of the adjusted sinusoid, $A$ is the amplitude, $\phi$ is the acrophase (phase in the maximum sine wave value), $\tau$ is the period (24 hours in this case) and $e(t)$ is the modelling error we tried to minimize (Fig. 1).

We imposed a minimum of 19 available hourly IAA values in order to apply the cosinor analysis. Otherwise, the Holter was discarded.

## 3.4. Statistical methods

Continuous variables are presented as median (interquartile range) unless otherwise specified. In order to estimate the association or dependence between two variables, Spearman correlation was used. Survival analysis was done by using the Kaplan-Meier estimator and log-rank test in order to compare commutative events. Prognostic value of IAA and cosinor-based parameters in predicting SCD was determined with univariate Cox proportional hazards analysis. For all tests, the null hypothesis was rejected for $p \leq 0.05$.

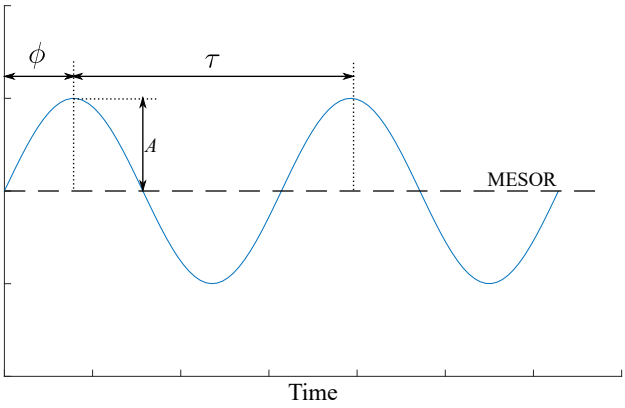


Figure 1. Sine wave together with the parameters that define the cosinor analysis.

## 4. Results

The cosinor analysis with 1-hour intervals could be performed in 76.8% of the patients (those for which IAA was computable at least in 19 intervals), while IAA analysis was analysable in 97.8% (there was no minimum number of processable segments).

Distributions of IAA and HR parameters computed in 1-hour intervals are presented in Fig. 2. Both parameters are affected by circadian rhythm in different ways: IAA distributions follow a biphasic oscillatory pattern, being minimal during the night period ($IAA_{01-02}$=0.43(0.482) $\mu$V), and maximal in the central hours of the day, getting its maximum value for the interval defined from 11.00 to 12.00h ($IAA_{11-12}$=0.931(1) $\mu$V)). Mean HR also presents a biphasic pattern, remaining at higher values during the hours of higher physical and mental activity (from 08:00 to 20:00 hours).

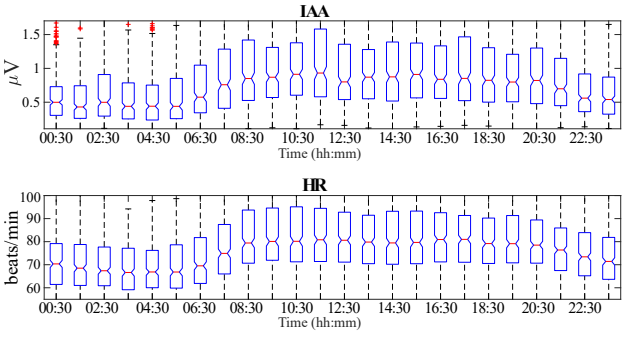


Figure 2. Distribution of IAA and HR in Holter-3 computed in 1-hour intervals.

The median correlation coefficients between IAA and HR were low and similar for the three Holters: $\rho_{H1}$ = 0.405 (0.397), $\rho_{H2}$ = 0.331 (0.453), $\rho_{H3}$ = 0.325 (0.397), for Holter-1, Holter-2 and Holter-3, respectively.

In Fig. 3, median IAA values computed from Holter-3 (blue) together with the cosinor model-based sinusoidal wave that fits the data, are represented.

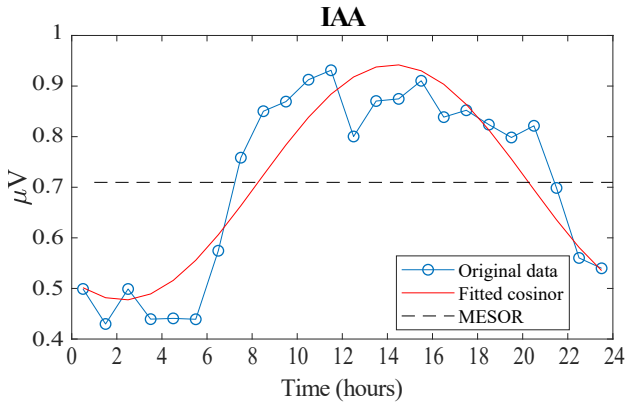


Figure 3. Sine function adjusted to the median IAA per hour in Holter-3 recordings obtained by Cosinor method.

The maximum IAA values of the adjusted sinusoidal wave took place between 13:50 and 14:31 hours. While cosinor amplitude $A$ was poorly correlated with IAA ($\rho_{IAA-A-1}$ = 0.353, $\rho_{IAA-A-2}$ = 0.3672, $\rho_{IAA-A-3}$ = 0.454), correlation between the IAA and the MESOR was stronger ($\rho_{IAA-M-1}$ = 0.6067, $\rho_{IAA-M-2}$ = 0.6926, $\rho_{IAA-M-3}$ = 0.7516).

Patients were classified in low- and high-risk groups according to IAA and MESOR by setting a risk threshold on the 75-th percentile of each variable. Survival analysis in the last available Holter showed that MESOR (but not IAA) was associated with SCD outcome in the study population (Table 2). The Kaplan–Meier curves for MESOR are shown in Fig. 4. The survival probability rate is significantly lower in high-risk patients (red) than in low-risk group (blue) at the end of the follow-up period.

Table 2. Association of IAA and MESOR parameters with sudden cardiac death in patients with heart failure.

| | **HaR** (95% CI) | **p-value** |
|---|---|---|
| IAA | 1.485 (0.611-3.61) | 0.38 |
| MESOR | **3.333** (1.377-8.063) | **0.008** |
| $MESOR_{LVEF<30\%}$ | **3.648** (1.222-10.891) | **0.02** |
| $MESOR_{LVEF\geq30\%}$ | 2.949 (0.651-13.350) | 0.16 |
| $MESOR^{max}$ | **4.068** (1.477-11.206) | **0.007** |
| $MESOR^{max}_{LVEF<30\%}$ | **3.780** (1.159-12.323) | **0.27** |
| $MESOR^{max}_{LVEF\geq30\%}$ | 7.350 (0.883-61.195) | 0.65 |

Two subgroups were defined according to their left ventricular ejection fraction (LVEF): those with reduced LVEF

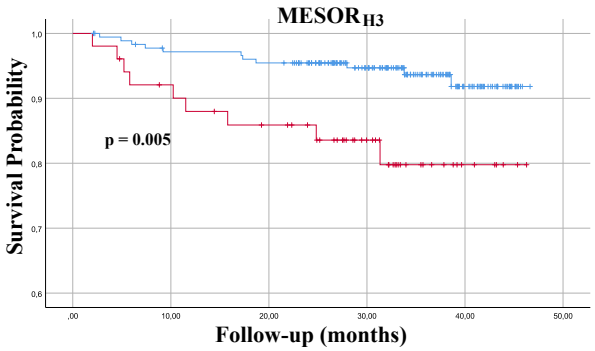


Figure 4. Kaplan-Meier curves for MESOR of IAA. In blue, survival probability curve of patients with low risk (MESOR-), in red, curve for high-risk patients (MESOR+).

(<30%) and with preserved LVEF (≥30%). The MESOR kept the predictive only in the reduced LVEF subpopulation. Finally, when considering the maximum MESOR value within the three Holter recordings for each patient, stratification performance improved as shown in Table 2.

## 5. Discussion and conclusion

Average TWA activity measured as the IAA is affected by circadian rhythms, as revealed by cosinor analysis, with maximum IAA values found in the central hours of the day. This pattern is not uniquely an effect of HR, as only a weak correlation between average HR and IAA was found, suggesting that TWA is affected by other factors different from HR. As expected, the MESOR parameter resulted to be strongly correlated with the IAA, in contrast to the cosinor amplitude. Indeed, the cosinor amplitude measures the intra-day variation of the index, while the MESOR represents a robust estimation of the average IAA value during the day.

In contrast with what was reported in previous studies performed in similar populations [2, 9], the IAA index was not significantly associated with SCD outcome. However, the MESOR computed from hourly IAA values was predictive of SCD (p = 0.008). This can be explained by the fact that IAA MESOR is a more robust estimate of the average TWA level. Note that, for IAA computation, there is no minimum number of required processable segments, so the final IAA could be computed in some cases with a very low number of processable segments, which may have affected negatively its performance. On the other hand, the restriction imposed for circadian analysis provoked that the MESOR could only be computed in 76.8% of the recordings.

In conclusion, TWA activity is modulated by circadian rhythms and the MESOR of the hourly IAA values can be considered as a novel, robust way for quantifying the average TWA activity in ambulatory recordings. This index is associated with SCD risk in the study mild-to-severe HF population.

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